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14. ABSTRACT

The purpose of this project is to identify the incidence of post traumatic hypopituitarism (PTH) in mild TBI and develop criteria for assessing which patients with a mid TBI are at risk for developing PTH. This study will also correlate the characteristics of the individuals with PTH by neorpsychological, neurophysiological and imaging testing as they relate to functional outcome. At 6 months post injury, patients will be screened for anterior pituitary function of the 56 mTBI subjects with IGF-1 results, of the 63 who completed the 6 month visit, the results fell below the lower threshold for 14% when using the Quest Diagnostics reference values. However, when the TBI was used, there were 31 subjects (55%) that met the criteria for hypopituitarism, with this finding, similar to that found in moderate-severe TBI population.

15. SUBJECT TERMS- Post traumatic hypopituitarism

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Introduction

This report outlines Dr. Masel's participation in the Mission Connect Mild Traumatic Brain Injury (mTBI) Translational Research Consortium during the time period of August 1, 2012 through July 31, 2013. Dr. Masel is the PI for Specific Aim 2.3, which is designed to study the diagnosis of post traumatic hypopituitarism after mTBI. The research activities of Specific Aim 2.3 are being conducted in collaboration with three other clinical projects in the Consortium: Specific Aims 2.1 (PI Levin), 2.2 (PI Papanicalaou/McCarthy), and 3.1.2-3.1.7 (PI Robertson) as the Integrated Clinical Protocol (ICP), which will use a shared group of subjects. For the Observational Studies (SA 2.1, 2.2, 2.3), the goal is to enroll 100 mTBI subjects that do not receive study drug (Specific Aim 3.1) and 100 subjects with Orthopedic Injuries (OI) for comparison. This project will use only the mTBI subjects, for whom we will determine the incidence of hypopituitarism following mTBI and develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening. We will also determine the relationship between post-traumatic hypopituitarism and functional outcome, cognitive recovery, and resolution of PCS at six months after mTBI. We will also examine the incidence of single and multiple pituitary hormone deficiencies. The clinical characteristics, MRI imaging results, EEG and MEG results of the subjects who have pituitary deficiency will be compared to those with normal pituitary function. The relationship between pituitary dysfunction and functional outcome, cognitive recovery, and resolution of PCS will be examined.

Body of report

SA #2.3: To study diagnosis of post-traumatic hypopituitarism after mTBI
SA #2.3.1: To determine the incidence of hypopituitarism following mTBI.
SA #2.3.2: To develop criteria for assessing which mTBI patients are at high risk for developing posttraumatic hypopituitarism and should have routine post-injury screening.

At the 6 Month Visit, mTBI subjects have blood samples drawn to examine six hormone levels that are indicative of anterior pituitary function, including somatomedin (IGF-1), thyroid stimulating hormone (TSH), thyroxine (Free T4), prolactin, and total cortisol in all subjects. Total testosterone is tested in male subjects, and 17 β-estradiols is tested in females.

As of July 15, 2013, 63 subjects completed the 6 month visit and had pituitary testing; of these 56 had IGF-1 levels available for analysis. To our knowledge, there is no ongoing study of this type (looking for pituitary dysfunction in mTBI), size or scope in the United States. Please see the Conclusion section for more detail. For a full discussion of subject screening and recruitment, please refer to Dr. Levin's report.

A summary of the mean, standard deviation, and ranges of the test results of pituitary function are presented in Table 1 below. The number of subjects falling outside the standard reference range results is also presented.

Table 1: Summary of Pituitary Test Results

Cortisol						Out of Range			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	10.1	4.4	3.4	22.0	0		0	
Male	41	10.6	4.4	2.4	41.0	1	2%	0	
All	63	10.4	4.3	2.4	63.0	1	2%	0	
Estradiols						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	21	75.0	56.6	11.8	207.4	1	5%	1	5%
IGF-1/Somatomedin						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	20	165.4	64.9	62.0	267.0	refer to IGF-1 Table			
Male	36	184.4	79.9	65.0	388.0				
All	56	177.6	74.8	62.0	388.0				
Prolactin						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	10.9	9.8	4.5	47.8	0		1	5%
Male	41	9.1	5.0	3.2	25.5	0		2	5%
All	63	9.8	7.0	3.2	47.8	0		3	5%
TSH						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	1.5	1.6	0.3	8.0	1	5%	1	5%
Male	41	1.7	1.2	0.5	6.2	0		3	7%
All	63	1.6	1.4	0.3	8.0	1	2%	4	6%
Thyroxine (Free T4)						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Female	22	1.0	0.1	0.8	1.3	0		0	
Male	41	1.0	0.2	0.8	1.3	1		0	
All	63	1.0	0.1	0.8	1.3	1		0	
Total Testosterone						**Out of Range**			
Gender	**n**	**mean**	**SD**	**Min**	**Max**	**Low**	**%**	**high**	**%**
Male	37	385.0	181.5	106.0	819.0	7	19%	0	

A separate table for the out-of-range values for IGF-1 is provided (Table 2 below), since these results are gender and age dependent. Table 2 indicates two parameters used to determine IGF-1 deficiency. The first (labeled: Standard Values) are the age/gender specific values used by Quest Diagnostics, the outside lab that does the IGF-1 test for Memorial Hermann Hospital-Texas Medical Center. However, IGF-I is a very rough estimate of the GH status of an individual and GH provocative stimulation testing, such as with the glucagon stimulation test (GST) is the only way to make a definitive diagnosis of growth hormone deficiency. The normal ranges for IGF-I are difficult to interpret, especially in individuals with TBIs because IGF-I can be influenced by many different variables. Therefore, many subjects who are GH deficient will have IGF-I levels in the normal range. The cutoff of an IGF-I of less than 175 (labeled TBI Values) is based on our study that correlated the response of the GST with the baseline IGF-I. (Zgaljardic et al., 2011). Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing.

Table 2: Subjects with Low IGF-1/Somatomedin Values

Standard* Reference Values				Standard Values		TBI Values**	
Age	**Female (ng/ml)**	**n**	**missing**	**Low**	**%**	**Low**	**%**
18-24 years	128-488 ng/mL	9	1	2	22%	2	22%
25-29 years	89-397 ng/mL	3		0		2	67%
30-34 years	71-352 ng/mL	1		0		0	
35-39 years	63-330 ng/mL	0	1				
40-44 years	58-318 ng/mL	5		1	20%	5	100%
45-49 years	54-307 ng/mL	2		0		2	100%
		20	2	3	15%	11	55%
Standard* Reference Values				**Standard Values**		**TBI Values****	
Age	**Male (ng/ml)**	**n**	**missing**	**Low**	**%**	**Low**	**%**
18-24 years	121-423 ng/mL	16	3	1		4	25%
25-29 years	112-402 ng/mL	6	1	2	33%	3	50%
30-34 years	89-350 ng/mL	5	1	1	20%	5	100%
35-39 years	77-323 ng/mL	3	2	0		2	67%
40-44 years	70-307 ng/mL	4	0	0		2	50%
45-49 years	66-296 ng/mL	2	1	1		4	200%
		36	8	5	14%	20	56%

*reference lab values **TBI values (Zgaljardic et al., 2011)

The missing IGF-1 results (six) shown in Table 2 are due to:

1. Incorrect IGF test entered by lab personnel (4)
2. Lab tests not done after sample was drawn (1)
3. Lab tests done but result cannot be located (1)

The lab order sheet for the 6 Month Visit has been revised to increase the accuracy of test entry by the lab personnel, and we are monitoring this very closely. The Research Team meets regularly with the CRU staff to ensure that they are familiar with all aspects of the protocol, and we have increased this interaction as well. To put this in perspective, the mTBI subjects get 6 lab tests for pituitary function at the 6 Month Visit. For the 63 enrolled mTBIs that have completed the 6 Month Visit, this would be a total of 378 tests. The errors in this group represent 1.85% of the tests done.

Key research accomplishments

- Dr. Masel has been an active participant in the Clinical Working Group as well as at the Partnering PI Quarterly meetings.

- Dr. Masel was an author on the following paper on the topic of post traumatic hypopituitarism in the past year: Masel, B. E., Bell, R. S., Brossart, S., Grill, R. J., Hayes, R. L., Levin, H. S., Rasband, M. N., Ritzel, D .V., Wade, C. E., DeWitt, D. S. (2012). Galveston Brain Injury Conference 2010: Clinical and experimental aspects of blast injury. Journal of Neurotrauma, *29*(12), 2143-2171.

- Dr. Masel presented on Post Traumatic Hypopituitarism to the Neurology Department at the University of Texas Medical Branch, June 5, 2013 and also to the North American Brain Injury Society in New Orleans, September 18-20, 2013

- Dr. Masel authored the following book chapter relative to post traumatic hypopituitarism in the past year: Masel, B E. Neuroendocrine Dysfunction after Traumatic Brain Injury. In: Nathan D. Zasler, Douglas I. Katz, and Ross D. Zafonte, editors. Brain Injury Medicine: Principles and Practice, 2nd Edition New York: Demos Medical Publishing; 2012. pp. 887-901.

Reportable outcomes

1. The analysis of pituitary hormones showed that of the subjects tested using the conservative testing values, 3 females (15%) and 5 males (15%) had low IGF-1 values indicative of Growth Hormone Deficiency. Using "TBI values (see reference above) 11 females (55%) and 20 males (56%) had low values for IGF-1.

2. IGF-1 deficiency was the most common finding

3. Testosterone deficiency was the second most common finding

4. Pituitary deficiencies are surprisingly common at six months following mild TBI. These findings are similar to those reported in moderate-severe TBIs.

Conclusion

In Year 5 of this project, enough mTBI subjects have completed their 6 Month Visit to provide very good preliminary data for analysis. We have found that post traumatic hypopituitarism is prevalent at the 6 month time point following a mTBI. A low IGF-1 (an indicator of low growth hormone levels) is the most common hormonal deficiency, with testosterone the next most common deficiency. Interestingly, these findings are consistent with the moderate-severe TBI hypopituitarism literature, where GH deficiencies are present in approximately 15-20% of those studied, and testosterone deficiency is approximately 5-10%. Of note, the moderate-severe TBI literature is mostly one year or more post injury, and we do not know if there would be some pituitary recovery in the population we are studying by month twelve.

We have started analyzing the data against the neuropsychological findings by Dr. Levin, and hope to identify what deficits and symptoms are specific to those with pituitary deficiencies. We clearly will produce a scientific publication on this. Due to the enormous number of mild TBIs (approximately 1 million every year in the US), we anticipate these findings will be of great interest to the scientific community, both civilian and military. Obviously, we will also work with other Consortium scientists to see if there is any commonality of hypopituitarism to EEG and/or imaging studies. Should there be positive findings, separate scientific publications will be produced.

Based on this preliminary data, we have been able to obtain private funds to do a small treatment trial for those who have pituitary dysfunction. Upon approval of the IRB, we will be able to solicit participation from subjects in this present research study. We will contact the subjects

who have been identified to be abnormal at 6 months, and rescreen them at 12 months (when spontaneous recovery of pituitary function will most likely have ceased), and then treat that deficiency.

It's obviously important to identify abnormalities. The more important question will be whether or not treatment of the abnormalities can change symptoms. Again, we anticipate a scientific publication from our results with recognition of the Consortium and CDMRP. If those results are positive, we will seek funding for a much larger multicenter definitive study. Should that study be positive, we believe this will change the standard of medical care for individuals with mild TBIs.

Reference

Zgaljardic, et al. (2011) Serum IGF-1 concentrations in a sample of patients with traumatic brain injury as a diagnostic marker of growth hormone secretory response to glucagon stimulation testing, *Clinical Endocrinology* 74, 365–369

Appendices

None